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PEPTIDE SWEETENING AGENTS

James M. Schlatter, Glenview, Ill., assignor to G. D. Searle & Co., Chicago, Ill., a corporation of Delaware

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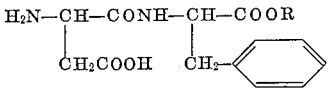
The present invention relates to novel compositions which are especially useful in view of their sweetening properties and to novel methods for the use of those compositions as sweetening agents.

The instant substances which exhibit this surprising sweetening property are dipeptide derivatives characterized by the following structural formula



wherein R is a lower alkyl radical.

Illustrative of the lower alkyl radicals denoted by the R term are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and the branched-chain groups isomeric therewith.

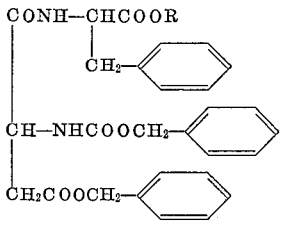
The surprisingly potent sweet taste of these dipeptide derivatives is completely unexpected and could not have been predicted from a consideration of their chemical structure. That property apparently is related to the polarity of the molecule as indicated by the fact that the compounds wherein R is hydrogen, i.e. the corresponding free carboxylic acids, are completely lacking in sweetness.

The sweetening property of the dipeptide substances is dependent also upon the stereochemistry of the individual amino acids, i.e. aspartic acid and phenylalanine, from which the dipetides are derived. Each of the amino acids can exist in either the D or L form, but it has been determined that the L-aspartyl - L - phenylalanine esters are sweet while the corresponding D - D, D - L, and L-D isomers are not. Combinations of isomers which contain the L—L dipeptide, i.e. DL - aspartyl - L - phenylalanine, L - aspartyl - DL - phenylalanine and DL - aspartyl-DL-phenylalanine, are sweet also.

The instant sweetening agents exhibit a remarkably greater potency than does sucrose. The sweetness of an aqueous solution of L - aspartyl - L - phenylalanine methyl ester, for example, can be detected at a concentration between 0.5–1% of that of sucrose. In other words, that dipeptide derivative is 100–200 times as sweet as sucrose. The corresponding ethyl ester is 25–50 times as potent as sucrose. It is apparent also that the sweetening agents of the present invention will be particularly useful to diabetics. These dipeptide esters furthermore do not result in the unpleasant after-taste characteristic of synthetic sweeteners such as saccharin and cyclamate. In consequence of their derivation from natural sources, i.e. naturally occurring amino acids, the instant sweeteners are devoid of toxic properties.

The instant dipeptide esters are conveniently manufactured by methods suitable for the coupling of amino acids. An especially preferred starting material is the aspartic acid derivative wherein the amino function is protected by a benzyloxycarbonyl group and the β-carboxy function by a benzyl ester group, and the α-carboxy group is converted to a p-nitrophenyl ester function. The preparation of that substance, i.e., N-benzoyloxycarbonyl - L - aspartic acid α-p-nitrophenyl, β-benzyl diester, is described by S. Guttmann, Helv. Chim. Acta, 44, 721 (1961). When that substance is allowed to react with a phenylalanine ester, displacement of the more reactive p-nitrophenyl ester

group occurs to afford the protected dipeptide of the following formula



wherein R is a lower alkyl radical as exemplified above. Removal of the N-benzyloxycarbonyl and O-benzyl protecting groups is conveniently effected by hydrogenolysis at atmospheric pressure and room temperature, utilizing palladium as the catalyst. Those processes are specifically illustrated by the reaction of N-benzyloxycarbonyl - L - aspartic acid α - p - nitrophenyl, β - benzyl diester with L-phenylalanine methyl ester to afford β - benzyl N-benzyl - oxycarbonyl - L - aspartyl - L - phenylalanine methyl ester and hydrogenolysis of that intermediate in aqueous acetic acid with palladium metal catayst to produce L-aspartyl - L - phenylalanine methyl ester.

The instant dipeptide sweetening agents are water soluble, stable substances which can be utilized in a variety of physical forms, e.g. as powders, tablets, syrups, etc. Liquid or solid carriers such as water, glycerol, starch, sorbitol, salt, citric acid and other suitable non-toxic substances can be utilized also. These compositions are particularly valuable as sweetening agents for edible materials. Examples of such materials are fruits, vegetables, juices, meat products such as ham or bacon, sweetened milk products, egg products, salad dressings, ice creams and sherbets, icings, syrups, cake mixes and beverages such as carbonated soft drinks and wines.

The invention will appear more fully from the examples which follow. These examples are set forth by way of illustration only and it will be understood that the invention is not to be construed as limited either in spirit or in scope by the details contained therein as many modifications both in materials and methods will be apparent from this disclosure to those skilled in the art. In these examples temperatures are given in degrees centigrade (° C.) and quantities of materials are expressed in parts by weight except where otherwise noted.

EXAMPLE 1

A solution of 88.5 parts of L-phenylalanine methyl ester hydrochloride in 100 parts of water is neutralized by the addition of dilute aqueous potassium bicarbonate, then is extracted with approximately 900 parts of ethyl acetate. The resulting organic solution is washed with water and dried over anhydrous magnesium sulfate. To that solution is then added 200 parts of N-benzyloxycarbonyl - L - aspartic acid α - p - nitrophenyl, β - benzyl diester, and that reaction mixture is kept at room temperature for about 24 hours, then at approximately 65° for about 24 hours. The reaction mixture is cooled to room temperature, diluted with approximately 390 parts of cyclohexane, then cooled to approximately —18° in order to complete crystallization. The resulting crystalline product is isolated by filtration and dried to afford β - benzyl N - benzyloxycarbonyl - L - aspartyl - L-phenylalanine methyl ester, melting at about 118.5–119.5°.

EXAMPLE 2

A solution of 6.15 parts of L - phenylalanine n - propyl ester hydrochloride in 20 parts of water is neutralized by the addition of dilute aqueous potassium bicarbonate, then is extracted with approximately 45 parts of ethyl acetate. That organic solution is washed with water and dried